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REMARKS

The Invention

In general, the invention features a mouse having an integrated transgene that includes a regulatory gene encoding a regulatory protein, and a transcription terminator. This mouse is useful in any number of genetic analyses.

The Office Action

Claims 1-17 are pending. Claims 15-17 are withdrawn as being drawn to nonelected subject matter. Claims 1-14 stand rejected for lack of enablement, and for obviousness in view of Friedrich et al. (Genes Devel. 5:1513, 1991) in view of one or more of St-Onge et al. (Nucleic Acids Res. 24:3875, 1996), Zhang et al. (Biochem. Biophys. Res. Comm. 227:707, 1996), and Bremer (Nucleic Acids Res. 20:5484, 1992). Claims 5-7 stand further rejected for indefiniteness. The declaration is objected to. Each of these matters is discussed below.

The Declaration

The Office states that the declaration is defective because it is directed to U.S.S.N. 09/002,046, of which the present application is a continuation. Applicant notes that "[a] continuation or divisional application filed under 37 CFR 1.53(b)...may be filed with a copy of the oath or declaration from the prior nonprovisional application." (MPEP

602.05(a). Thus, the declaration submitted in the present application should not be deemed defective, and reconsideration is respectfully requested.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-14 are rejected for lack of enablement. According to the Office, it would require undue experimentation to use the claimed mice. Applicant respectfully traverses this rejection.

The claims are directed to a mouse having a transgene integrated into an endogenous gene of the mouse. The transgene itself includes a regulatory gene encoding a regulatory protein, and a transcription terminator. Additionally, the transgene has integrated into the endogenous gene in such a way that the regulatory gene is positioned for expression under control of the promoter of the endogenous gene.

The issue raised by the Office is that the claims encompass mice having no phenotype at all. The Office states that the specification "fails to teach how to use the mice with the claimed genotype but without any phenotype. Therefore, one skilled in the art would not know how to use the invention."

Applicants first note that because of the mutagenic capacity of the transgene, many lines of mice do have a readily identifiable phenotype. To date, applicants have isolated 27 lines of mice as presently claimed. Of these lines, applicants have tested six with a limited set of assays, and, of these, three have a measurable phenotype. Thus, it is

applicants' position that the claims are enabled to the full scope, even if one could not use the mice lacking a phenotype.

Moreover, contrary to the position taken by the Office, the specification does teach how to use the claimed mice, regardless of whether there is a readily identifiable phenotype. For example, starting at page 17, line 23, the specification describes the use of a regulatory gene encoding an exemplary regulatory protein, rtTA:

> As described above, the fusion gene, rtTA, is produced only in cells expressing the gene mutated by a retroviral insertion. The conditional nature of rtTA synthesis allows the specific tagging of insertion-containing cells through a binary mammalian system, such as a binary mouse system. According to this technique, mice carrying the retroviral vector of the present invention may be mated to mice containing a marker gene under the control of the rtTA-dependent promoter. In offspring containing both transgenes, that marker will only be produced in cells expressing rtTA, and only in the presence of tetracycline derivatives.

Later, the specification describes other uses of the mice of the claimed invention, such as for the conditional ablation of cell lineages expressing mutant genes (page 18, line 13, to page 19, line 21), the spatiotemporal phenotypic analysis of disrupted genes (page 19, line 22, to page 20, line 21), and the conditional expression of genes of interest (page 22, line 25, to page 24, line 14).

In each of the foregoing examples, mice of the claimed invention can be employed even if there is no identifiable phenotype. Indeed, one of the great values of the mice of the claimed invention is to aid in determining the function of the gene into which the transgene is integrated when the phenotype is not known.

In sum, the two important characteristics of the mice are (i) the expression of the regulatory gene from the promoter of the endogenous gene, and (ii) the mutation of the endogenous gene. While an identifiable phenotype may be desirable, it is by no means required, as the foregoing discussion demonstrates. Accordingly, applicant respectfully requests reconsideration of the rejection of claims 1-14 for lack of enablement.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 5-7 are further rejected because it is unclear whether, in claim 5, the term "another gene" refers to an endogenous gene or a transgene. Applicant has amended claim 5 to recite "a second transgene" and this rejection may now be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 1-14 are yet further rejected as being obvious over Friedrich et al. in view of one or more of St-Onge, Zhang, and Bremer. Applicant respectfully traverses this rejection.

Claim 1, the sole independent claim, recites a mouse having a transgene that has integrated into an endogenous gene of the mouse. Significantly, the transgene itself includes (i) a regulatory gene encoding a regulatory protein, and (ii) a transcription terminator, at which site transcription terminates.

In order to establish a *prima facie* case of obviousness, the Office has the burden of showing that a combination of the references teaches or suggests every claim

limitation. In the present case, the Office fails to indicate which reference teaches or suggests the claimed transcription terminator. Applicant has reviewed the cited references and submits that no combination could teach the claimed mice because each reference fails to disclose such a transcription terminator. Friedrich, the primary reference, fails to mention transcription termination sequences or their desirability, thereby also failing to suggest or provide any motivation for inserting these sequences into a mouse. Moreover, the deficiencies in Friedrich are not cured by the other cited references. St-Onge discloses mice expressing a *tetR/VP16* regulatory gene. Zhang discloses the use of green fluorescent protein as a reporter protein. And Bremer simply discloses the VDE restriction site and VDE-mediated digestion. None of these references teaches termination site sequences or mentions the use of such sequences in the generation of transgenic mice.

In contrast, each of the pending claims recites a mouse having a transgene that contains a transcription termination site sequence. As described in the specification, for example, at page 17, such termination sequences provide special advantages. Notably, the use of these sequences prevents read-through transcription of flanking cellular sequences when the terminator is integrated into a host chromosome. In addition, the use of such transcription termination sites provides significantly increased mutagenic capability by blocking potential bypassing of insertions through alternative splicing events that make use of fortuitous, downstream chromosomal splice sites.

Claims 1-14 are not suggested by the prior art, and applicant requests reconsideration and withdrawal of the § 103 rejection.

Initialed Form 1449

Applicant notes that the Form 1449 submitted with the application on October 17, 2001 has not been initialed and returned, and such action is respectfully requested.

CONCLUSION

Applicant submits that the claims are now in condition for allowance, and such action is respectfully requested. If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 23 December 2003

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